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10/753,068	01/08/2004	Bao-Lu Chen	PP-17853-005	6547

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EXAMINER	
ROOKE, AGNES BEATA	
ART UNIT	**PAPER NUMBER**
1653	

DATE MAILED: 10/05/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/753,068	CHEN ET AL.	
	Examiner	Art Unit	
	Agnes B Rooke	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-32 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-32 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on 08 January 2003 is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 20040804.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-32 are pending.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-32 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. These claims contain subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

In the instant case, Claim 1 refers to TFPI and "TFPI-variant." The specification describes TFPI as tissue factor pathway inhibitor, and states that TFPI variant differs from TFPI by the addition of an alanine residue at the amino terminus ("ala-TFPI"). See page 2, paragraph 4, line 6.

Furthermore, specification refers to TFPI or "TFPI variants." See page 2, paragraph 6, line 2. Thus, it is not clear if the "Ala-TFPI variant" is the only variant claimed, or if there are other variants of TFPI suggested in Claim 1.

Moreover, specification refers to TFPI variants that include analogs and derivatives of TFPI, as well as fragments of TFPI. See page 9, paragraph 26.

Therefore, definition of TFPI variant must be clarified in the specification, since the word "include" is an open-ended phrase and does not properly define the invention. Consequently, the specification does not enable any person skilled in the art to which it pertains, to make the invention commensurate in scope with Claims 1-30, since they are very broadly defined.

Claims 1-32 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. Claims contain subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, to make and/or use the invention. In the instant case, the specification does not reasonably provide enablement for a method of increasing stability of TFPI variants, since TFPI variants are not specifically defined.

According to Claim 1, it can be interpreted that claimed aqueous composition comprising TFPI or TFPI variant refers to all TFPI variants in all aqueous compositions. Also, it is well known in the art, that stability of individual polypeptides, such as TFPI or its variants, is very specific to an appropriate physical and chemical condition, such as different pH of a buffering agent, different osmolarity, and other agents and factors. Thus, claiming a composition, which improves stability for all TFPI variants would not be adequate, and would not enable one skilled in the art to make and/or use the invention.

The factors considered in determining whether undue experimentation is required, are summarized in *In re Wands* (858 F2d, 731,737, 8 USPQ 2d 1400,1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the breadth of the claims, the presence or absence of working examples, the state of the prior art and

relative skill of those in the art, the predictability or unpredictability of the art, nature of the art, the amount of direction or guidance presented, and the amount of experimentation necessary.

1. The breadth of the claims:

The breadth of the claims is broad and encompasses unspecified TFPI variant, or variant which is about 70% or more homologous to TFPI (SEQ ID NO:1), which variants are not adequately described or demonstrated in the specification. It is clear that there could be many variants that are about 70% or more homologous to the TFPI.

2. The presence of absence of working examples:

The specification indicated Ala-TFPI as a variant, and the working Examples: 2, 3, 4, 5, 6, 7, and 8 used only Ala-TFPI in their experiments. However, there were no other working examples that included other TFPI variants, except ala-TFPI. See pages 26-36.

3. The state of the prior art and relative skill of those in the art:

The related art indicates that other TFPI variants are known in the art. See pages 9-11. Even though the relative skill in the art is high, the general knowledge and level of the skill in the art do not supplement the omitted description of other TFPI variants that Applicant tries to claim. Thus, to be considered enabling TFPI variants, the specification needs to provide specific examples of TFPI variants, and their specific sequence homology to TFPI (SEQ ID NO:1).

4. Predictability or unpredictability of the art:

Claims encompass unidentified number of TFPI variants, or TFPI variant that is about 70% or more homologous to TFPI (SEQ ID NO:1). However, the identities of those

variants are not disclosed in the specification, thus it is not predictable what TFPI variants are claimed in the application.

5. The amount of direction or guidance presented and the quantity of experimentation necessary:

Claims are directed to TFPI variant, or variant that is about 70% or more homologous to TFPI (SEQ ID NO:1), or ala-TFPI. However, in Materials and Methods section of the application, working Examples: 2, 3, 4, 5, 6, 7, and 8 used only ala-TFPI in their experimentation, and not other variants, such as variant with about 70% or more homology to TFPI (SEQ ID NO:1). See pages 26-36. Since the specification does not provide sufficient teachings on the identities of TFPI variants other than ala-TFPI, it is necessary to have additional guidance and carry out further experimentation to identify and specify various TFPI variants that apply specifically to this invention.

6. Nature of the Invention:

The scope of the claims includes: unidentified number of TFPI variants, TFPI variant with about 70% or more homology to TFPI (SEQ ID NO:1) and ala-TFPI. The working examples only used ala-TFPI, however specification has not identified nor has demonstrated the effects of different TFPI variants on the stabilized composition claimed as the invention. Thus, the disclosure does not enable one skilled in the art to make the invention for the reasons discussed above.

In summary, the scope of the claims is broad, while the working examples do not demonstrate the claimed TFPI variants, and the teaching in the specification is limited.

Therefore, it is necessary to have additional guidance and to carry out further experimentation to identify specific TFPI variants claimed in this invention.

Furthermore, TFPI variants do not meet the written description provision of 35 U.S.C. 112, first paragraph. *Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111, states that "applicant must convey with reasonable clarity to those skilled in the art, that as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." Id. at 1117.

In the instant case, TFPI variant other than Ala-TFPI, and variant with about 70% or more homology to TFPI (SEQ ID NO:1) have not been described and disclosed.

Moreover, the listing of variants must be provided and an appropriate experimentation must be taught, since conception cannot be achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of preparation. *Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) ; Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. Also, claims were found unpatentable due to lack of written description for the broad class, and because one could not describe what one has not conceived. *Fiddes v. Baird*, 30 USPQ2d 1481,1483.

In the instant case, one skilled in the art cannot envision all the contemplated compounds based upon the general suggestion of TFPI variants in the specification. See pages 9-12. The listing of specific TFPI variants claimed must be provided and an appropriate experimentation for the variants must first be performed and then taught.

Also, an adequate written description requires more than a mere statement that TFPI variant is part of the invention or a reference to a potential stabilized composition that contains those variants, and in the instant case the written description does not satisfy this requirement.

Applicant is reminded that the written description provision of 35 U.S.C. 112 is severable from its enablement provision. *Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d at 1115. Also, Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, first paragraph, "Written Description" Requirement, Federal Register, Vol. 64, No. 244, pages 71427-71440, Tuesday December 21, 1999.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Here, in the first sentence, Applicant must spell out the full name of the TFPI at the first instance. Thus, proper clarification is required.

Further, Claims 1, 2, 3, and 7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The metes and bounds of the term "TFPI variant" is not clear and too broad, and thus specific examples of TFPI variants claimed must be provided. It is well known that structural variants have distinct

biological, and functional features, therefore further clarification of "TFPI variant" is required.

Claim 2 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicant states that "TFPI variant is about 70% or more homologous to TFPI (SEQ ID:1)." Here, Applicant must specify an adequate sequence homology to the TFPI (SEQ ID:1).

Claim 8 and 9 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Here, Applicant uses the phrase *"enriched,"* which is indefinite and vague. Thus, proper definition of "enriched" is required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under

37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 USC 103(c) and potential 35 USC 102(e), (f) or (G) prior art under 35 USC 103(a).

The instant invention claims an aqueous composition comprising tissue factor pathway inhibitor, TFPI or TFPI variant, a solubilizing agent and an antioxidant.

Claims 1-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Peterson et al. (U.S. 2003/0092627). Petersen et al. teach a pharmaceutical composition (when is single-preparation form) consisting essentially of factor VIIa and factor XIII, and/or **stabilizer**, and/or a detergent, and/or a neutral salt, and/or an **antioxidant**, and/or a preservative, and/or a protease inhibitor, and/or **TFPI inhibitor**. See page 10, paragraph 118, 119, and page 11 paragraph 121. Petersen et al. do not teach a single composition comprising TFPI variants and antioxidants in a pharmaceutical composition.

A person of ordinary skill in the art at the time the invention was made would have been motivated to make the pharmaceutical composition comprising a stabilizer, an antioxidant, and TFPI, as per teachings of Petersen at al., because the idea of combining TFPI, a stabilizer and an antioxidant in one composition was clearly disclosed in Petersen at al.

Hence, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify teaching of Petersen et al. and make a composition comprising TFPI, a solubilizing agent, and an antioxidant.

Claims 1-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chen et al. (U.S. 6,525,102) in view of Kosoglou et al. (U.S. 2002/0147184 A1).

Chen et al. (U.S. 6,525,102) teach a stabilized liquid pharmaceutical composition comprising tissue factor pathway inhibitor (TFPI) or variant thereof, a stabilizing agent, a buffering agent, wherein the stabilizing agent is arginine in its free base form and the buffering agent is succinic acid. See Claims 6-12, 21-24. These teachings meet the limitations of the instant claims, directed to the stabilized pharmaceutical compositions of TFPI, TFPI variant, a stabilizing agent, such as arginine, a buffering agent, and a succinic acid. Chen *et al.* (U.S. 6,525,102) lack an antioxidant. See page 12.

Kosoglou *et al.* (U.S. 2002/0147184 A1) teaches compositions, therapeutic combinations and different methods useful in treating vascular conditions and lowering plasma levels sterols. See page 1, paragraph 1. Above all, the aforementioned compositions comprise tissue factor pathway inhibitor (TFPI) and at least one antioxidant. See Claims 27 and 42. Claim 27, teaches composition wherein the factor Xa inhibitor is selected from the group consisting of tissue factor pathway inhibitor (TFPI), and Claim 42 teaches that the composition further comprises at least one antioxidant. Claims 27 and 42 teach TFPI and an antioxidant in one composition. Furthermore, teachings of Kosoglou *et al.* (U.S. 2002/0147184 A1) are analogous with

the instant invention, since in both instances, TFPI and an antioxidant are present in one composition. However, the reference does not teach TFPI variants and an antioxidant in one composition.

A person of ordinary skill in the art at the time the invention was made would have been motivated to combine teachings of Chen et al. (U.S. 6,525,102) and Kosoglou *et al.* (U.S. 2002/0147184 A1) because of the need to have a protein, such as TFPI, in a stable form to retain its bioactivity. In both cases, stabilizing agent and an antioxidant was added to a composition to stabilize TFPI.

The rejections under 35 U.S.C. 103(a) above are consistent with case law. Applicants are referred to *In re Kerkoven*, 205 USPQ 1069, in which it was shown to be *prima facie* obvious to combine two compositions, each of which was taught by the prior art to be used for that very same purpose. *Ex parte Quadranti*, 25 USPQ2d 1071 also sets forth the precedent, where the use of materials in combination, each of which is known to function for the intended purpose is generally held to be *prima facie* obvious.

Hence, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use analogous prior art to include an antioxidant in a composition containing TFPI.

Claims 14 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chen *et al.* (U.S. 6,525,102) in view of Kosoglou *et al.* (U.S. 2002/0147184 A1) taken further with Takruri (U.S. 5,272,135).

Takruri (U.S. 5,272,135) teaches stabilizing formulations for methionine containing polypeptides by addition of methionine to inhibit oxidation of the methionine residue(s). Column 2, line 60-68. The added methionine stabilizes the preparation containing a polypeptide by inhibiting the rapid oxidation of the methionine residue(s) to methionine sulfoxide. Column 2, line 60-68.

A person of ordinary skill in the art at the time the invention was made would have been motivated to substitute methionine as the antioxidant with TFPI in the composition of Chen *et al.* (U.S. 6,525,102), because Takruri (U.S. 5,272,135) establishes methionine would act as an antioxidant and improve stability by reducing the oxidation of a polypeptide chain.

Hence, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use methionine as antioxidant in a composition containing TFPI or its variants.

Claims 6-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chen *et al.* (U.S. 6,525,102). Chen *et al.* teach that addition of oxygen removal by nitrogen purging and degassing decreases the percentage of the methionine oxidative species and improves protein stability. See Example 2. However, the reference does not teach oxygen removal in a composition containing TFPI or TFPI variants.

A person of ordinary skill in the art at the time the invention was made would have been motivated to remove oxygen from the composition of TFPI because the

procedure would reduce the percentage of the methionine oxidative species, and thus improve the stability of TFPI in a composition.

Hence, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to design a stabilized pharmaceutical composition comprising TFPI, and an antioxidant, such as an oxygen displacement gas.

In conclusion, it would have been obvious to one skilled in the art to use teachings of Chen *et al.*, Kosoglou *et al.*, and Takruri to include TFPI and an antioxidant together in a stabilized pharmaceutical composition.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Agnes Rooke whose telephone number is 571-272-2055. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached on 571-27-0925. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for unpublished applications is available through Private PAIR or Public PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you

have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

AR

JON WEBER
SUPERVISORY PATENT EXAMINER